discrete set of independent rules, no matter how complex, is a task that can, at best, result in a first order approximation of the process. This places an inherent limitation on the quality of feedback that can be provided. As a consequence it is extremely difficult to develop feedback that explicitly takes into account all information available on the patient. One might speculate that the lack of widespread acceptance of such systems may be due to the fact that their recommendations are often rejected by physicians. These systems must be made more valid if they are to enjoy widespread acceptance among physicians.

The proposed MENTOR system is designed to address the significant problem of adverse drug reactions by means of a computer-based monitoring and feedback system to influence physician decision-making. It will employ principles of artificial intelligence to create a more valid system for evaluating therapeutic decision-making.

The work in the MENTOR project is intended to be a collaboration between Dr. Blaschke at Stanford and Dr. Speedie at the University of Maryland. Dr. Speedie is spending the 1983-84 academic year on sabbatical with Dr. Blaschke in the Division of Clinical Pharmacology at Stanford University. While at Stanford, Dr. Speedie has been strengthening his expertise in the area of artificial intelligence and establishing links in the AI community. Dr. Speedie has begun work on the development of the MENTOR system pilot project on the SUMEX-AIM facility. Over the past nine months, Drs. Blaschke and Speedie have worked closely together to design the MENTOR project. The blend of previous experience, medical knowledge, computer science knowledge and evaluation design expertise they represent is vital to the successful completion of the activities in the MENTOR project.

C. Highlights of Research Progress

The MENTOR project was initiated in December 1983. The work to date has consisted of preparation of a grant proposal for the National Center for Health Services Research and initial exploration of the problem of designing the MENTOR system. Work has begun on constructing a system for monitoring potassium in patients with drug therapy that can adversely affect potassium levels.

E. Funding Support

Application for grant support is pending.

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations and Program Dissemination via SUMEX

This project represents a collaboration between faculty at Stanford University Medical Center and the University of Maryland School of Pharmacy in exploring computer-based monitoring of drug therapy. SUMEX, through its communications capabilities, will facilitate this collaboration when Dr. Speedie returns to the University of Maryland in August of 1984.

B. Sharing and Interactions with Other SUMEX-AIM Projects

Interactions with other SUMEX-AIM projects has been on an informal basis. Personal contacts have been made with individuals working on the ONCOCIN project concerning issues related to the formulation of the previously mentioned proposal. We expect interactions with other projects to increase significantly once the groundwork has

been laid and issues directly related to AI are being addressed. Given the geographic separation of the investigators, the ability to exchange mail and programs via the SUMEX system as well as communicate with other SUMEX-AIM projects is vital to the success of the project.

C. Critique of Resource Management

To date, the resources of SUMEX have been fully adequate for the needs of this project. The staff have been most helpful with any problems we have had and we are fully satisfied with the current resource management. The only concern we have relates to the state of the documentation on the system.

III. RESEARCH PLANS

A. Project Goals and Plans

To accomplish the goals described in the Project Rationale, a number of tasks will be undertaken. The short-term task is to develop an initial prototype of the medical knowledge base and inference mechanisms for arriving at appropriate therapy monitoring decisions. This initial work focuses on monitoring for hyperkalemia and the decision-making process with respect to ordering potassium levels. We will then attempt to construct a system combining frames and rules that will model this process. The purpose of this initial exercise is to explore the problems involved in constructing an AI system that meets the needs of drug therapy monitoring and to establish development guidelines for the larger project.

The long-range plans for the MENTOR project depend on the outcome of the funding decision. However, assuming a favorable decision, the full project has the following goals:

1. Implement a prototype computer system to continuously monitor patient drug therapy in a hospital setting. This will be an expert system that will use a modular, frame-oriented form of medical knowledge, a separate inference engine for applying the knowledge to specific situations and automated collection of data from hospital information systems to produce therapeutic advisories.

2. Select a small number of important and frequently occurring medical settings (e.g., combination therapy with cardiac glycosides and diuretics) that can lead to therapeutic misadventures, construct a comprehensive medical knowledge base necessary to detect these situations using the information typically found in a computerized hospital information system and generate timely advisories intended to alter behavior and avoid preventable drug reactions.

3. Select and test several methods of formulating and providing advisories to physicians in order to find an optimal method of feedback that is acceptable and useful to physicians and is feasible to implement.

4. Design and begin to implement an evaluation of the impact of the prototype MENTOR system on physicians' therapeutic decision-making as well as on outcome measures related to patient health and costs of care.

B. Justification and Requirements for Continued SUMEX Use

This project needs continued use of the SUMEX facilities for two reasons. First is that it provides access to an environment specifically designed for the development of AI

systems. The MENTOR project focuses on the development of such as system for drug monitoring that will explore some neglected aspects of AI in medicine. Access to SUMEX is necessary for timely development of the MENTOR system, as well as advice and assistance in the design and development of a well-designed and efficient system. Access to SUMEX is also necessary to support the collaborative effort in this project as described previously.

C. Needs and Plans for Other Computing Resources Beyond SUMEX-AIM

A major long-range goal of the MENTOR project is to implement this system on a independent hardware system of suitable architecture. It is recognized that the full monitoring system will require a large patient data base as well as a sizeable medical knowledge base and must operate on a close to real-time basis. Ultimately, the SUMEX facilities will not be suitable for these applications. Thus we intend to transport the prototype system to a dedicated hardware system that can fully support the the planned system and which can be integrated into the SUMC Hospital Information System. However, no firm decisions have been made about the requirements for this system since many specification and design decisions remain to be made.

D. Recommendations for Future Community and Resource Development

In the brief time we have been associated with SUMEX, we have been generally pleased with the facilities and services. However, it is evident that disk space is a critical factor in the functioning of the facility. It would seem wise to increase disk storage in order to meet the needs of the users. Our experience also indicates that an attempt needs to be made to organize and update the documentation associated with the various SUMEX systems. Being new users, we found that paths to useful software was somewhat longer than one might expect. An expanded introduction to the system that, at least, briefly described the software available on SUMEX would be useful.

II.A.3.3. Protein Secondary Structure Project

Protein Secondary Structure Project

Robert M. Abarbanel, M.D.
Section on Medical Information Science
University of California Medical Center
University of California at San Francisco

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

Development of a protein structure knowledge base and tools for manipulation of that knowledge to aid in the investigation of new structures. System to include cooperating knowledge sources that work under the guidance of other system drivers to find solutions to protein structure problems. Evaluations of structure predictions using known proteins and other user feedbacks available to aid user in developing new methods of prediction.

B. Medical Relevance and Collaboration

Many important proteins have been sequenced but have not, as yet, had their secondary or tertiary structures revealed. The systems developed here would aid medical scientists in the search for particular configurations, for example, around the active sites in enzymes. Predictions of secondary structure will aid in the determination of the full "natural" configuration of important biological materials. Development of systems such as these will contribute to our knowledge of medical scientific data representation and retrieval.

C. Highlights of Research Progress

The prediction of beta-alpha protein structures is complete. The system was developed on a VAX 11/750 at the University of California, San Francisco, to allow researchers to describe patterns of amino acid residues that will be sought in the sequences under study. The presence or absence of these "primary" patterns are then combined with other measures of structure, like hydrophobicity, to suggest possible alpha helix or beta sheet or turn configurations.

The segments of a sequence between turns are then analyzed to determine the allowable extent of the possible secondary structure assignments. Any segments remaining are then used to generate all possible complete structures. Only two beta strands with the character of sheet edges are allowed in any prediction. This hierarchical generation and pruning results in nearly 95% turn prediction accuracy, and excellent delimiting of helices and sheets. In some cases, one and only one secondary structure is predicted.

Research in Progress -- At this time, work is under way to extend this α/β assignment work to a set of cancer causing viral proteases. These proteins are believed to be of the α/β type. The set of homologous sequences under study introduces new problems and insight into the problems of structural assignment. If one is to believe that major structural features are conserved across a primary sequence homology, then methods must be developed for predicting structure when possibly conflicting signals come

from individual sequences in a set. Other sets of proteins, like the Triose Phosphate Isomerases, will help to develop this knowledge.

Dr. F. Cohen is using the pattern matching and rules system on a regular basis to develop a means for predicting turns in proteins of the all-α and all-β classes. His use of the system stimulates simultaneous development of improved rules support and explanation facilities.

D. List of Relevant Publications

The first paper on $\beta\alpha\beta$ protein structures has been published: Cohen, F.E., Abarbanel, R.M., Kuntz, I.D. and Fletterick, R.J.: ***Secondary structure assignment for α/β proteins by a combinatorial approach***, Biochemistry, 22, pp 4894-4909, (October 1983). At this time, another paper on prediction of "turns" in several classes of proteins is under preparation. Similar pattern matching tools are implemented in the QUEST program written in Mainsail and supported commercially by Intelligenetics, Inc. This program converts patterns given by users into and/or trees of finite state machines: Abarbanel, R.M., P.R. Wieneke, E. Mansfield, D.A. Jaffe, and D.L. Brutlag, ***Rapid searches for complex patterns in biological molecules***, Nucleic Acids Research, 12, pp 263-280, (January 1984).

E. Funding Support

Title:	Protein Structural Knowledge Engineering
Principal Investigator:	Robert M. Abarbanel, M.D.
Funding Agency:	National Library of Medicine, N. I. H.
Grant ID Number:	1 R23 LM 03893-01
Total Award:	4/1/83 to 3/31/86
	$ 104876 Total Direct Costs
Current Period:	4/1/84 to 3/31/85
	$ 40900 Total Direct Costs

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations

None.

B. Sharing and Interactions with SUMEX Projects

This project is closely allied with the MOLGEN group, both in computer and scientific interests. Some pattern matching methodology created for the protein data base has been adopted and used in the various DNA knowledge bases. The principal persons in the MOLGEN group have contributed to this project's use and understanding of knowledge base software and resources.

C. Critique of Resource Management

Work continues on the UNIX systems at the University of California, San Francisco. SUMEX has been used primarily for communications with other researchers. At some future date it is expected that the knowledge based system will be ported to SUMEX on one or more of the LISP machines available.

Resource management remains excellent. The staff are friendly and responsive.

Network access, bulletin boards and the mail system have provided a means to collaborate with others doing related work locally as well as in Europe. SUMEX-AIM staff have been most helpful in getting this project started on the Dolphin workstations and in providing an environment where new tools have been made available for use.

III. RESEARCH PLANS

A. Project Goals and Plans

Near Term -- Development of "parallel" assignment techniques to allow homologous sequences to aid in the prediction of structure for one or more unknown sequences. Completion of Lisp system providing a friendly environment for structure exploration. This will involve merging sequential rule interpretation with back chaining. Both these systems will be able to invoke the running of patterns of amino-acid residues against known or unknown sequences. Along with the capacity to manipulate the order of application of rules, the system will allow undoing of decisions during processing, and explanation of reasoning during structure assignment. These are all features of knowledge engineering that are not present in the current system.

Long Term -- Expansion of techniques used for α/β prediction to other classes of proteins. Improvement of user interfaces to allow use of this sequence analysis system for problems of homology and energetics. Use of bit-map graphics and an interface to the line-drawing color graphics at UCSF to enhance the user's view of the data and possibly enhance the development of new knowledge sources for application to these problems. Several areas of current interest may contribute here: distance geometry, docking, energy minimization, and multi-sequence homologies.

B. Need for Resources

SUMEX Resources -- The availability of UNIX (TM) under SUMEX-AIM control will greatly aid in the transferability of existing algorithms. The environment of knowledge base tools and people is the primary motive for doing this work using SUMEX. Access to both established and developing systems aids this project in setting down standards of excellence, forward thinking about computing tools and methodologies, and active exchange of techniques and ideas. The close collaboration with the MOLGEN researchers is particularly useful in this regard.

Other Computing Resources -- A soon to be established network connection with the Computer Graphics Laboratory at UCSF will provide access to 1) the latest in protein structural information, and 2) color line drawing graphics facilities for evaluation and display of this projects product. A real time display using color graphics will become a possibility. Lisp based machines soon to be acquired at UCSF will allow direct collaboration with efforts at SUMEX on knowledge based software for protein structure determination.

C. Recommendations

No changes from last year's report: First and most important -- EXPAND the computing power available to SUMEX users. Facilitate networking with other computing environments like the Computer Graphics Laboratory at UCSF so that protein structural information may be exchanged and their hardware for 3D structure display may be utilized as a part of a complete biological structures analysis system.

Second -- Provide whatever hand-holding is necessary to expose SUMEX-AIM users

to other facilities available on the network. This will allow a project to find its best home in the SUMEX environment.

II.A.3.4. PROTEAN Project

PROTEAN Project

Oleg Jardetzky
Nuclear Magnetic Resonance Lab, School of Medicine
Stanford University

Bruce Buchanan
Computer Science Department
Stanford University

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale The goal of this project is two-fold: (a) use existing AI methods to aid in the determination of the 3-dimensional structure of proteins in solution (not from x-ray crystallizing proteins), and (b) use protein structure determination as a test problem for experiments with the AI control structure known as the Blackboard Model.

B. Medical Relevance The molecular structure of proteins is essential for understanding many problems of medicine at the molecular level, such as the mechanisms of drug action. Using NMR data from proteins in solution will speed up the determination.

C. Highlights of Progress This project is just getting started. There is no substantial progress to date.

E. Funding Support

Grant applications submitted to the NSF:

Title: Interpretation of NMR Data from Proteins
Using AI Methods

PI's: Oleg Jardetzky and Bruce G. Buchanan

Agency: National Science Foundation

Total Amount: $969,991.

Dates: Apr 1, 1984/March 31, 1989

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations Several members of Prof. Jardetzky's research group are involved in this research.

B. Interactions with other SUMEX-AIM projects

Robert Langridge is visiting in the HPP this academic year and has been participating in discussions. Carroll Johnson has been helpful in making ORTEP available and answering questions about it.

C. Critique of Resource Management

The SUMEX staff has been most cooperative in helping get this project started. Because the terminals available in SMRL for our use are IBM PC's, we needed considerable help with communications.

III. RESEARCH PLANS

A. Goals & Plans

Our long range goal is to build an automatic interpretation system similar to CRYSALIS(which worked with x-ray crystallography data). In the shorter term, we are building interactive programs that aid in the interpretation. We are putting together building blocks now and are designing the control structure. We plan to purchase a high resolution graphics display workstation as soon as our exploratory investigations indicate the expense is justified.

B. Justification for continued SUMEX use

We will continue to use SUMEX for developing the AI methods. We need Interlisp to implement the Blackboard model and knowledge structures most flexibly and quickly.

C. Need for other computing resources

We believe we must purchase a graphics workstation for display of partial results.

D. Recommendations

With the increased number of personal computers and workstations in the community, it would be desirable to provide more staff to integrate these machines with SUMEX and centralize sharing of software across the community.

II.A.3.5. Ultrasonic Imaging Project

Ultrasonic Imaging Project

James F. Brinkley, M.D.
W.D. McCallum, M.D.
Depts. Computer Science, Obstetrics and Gynecology
Stanford University

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

The long range goal of this project is the development of an ultrasonic imaging and display system for three-dimensional modelling of body organs. The models will be used for non-invasive study of anatomic structure and shape as well as for calculation of accurate organ volumes for use in clinical diagnosis. Initially, the system has been used to determine fetal volume as an indicator of fetal weight; later it will be adapted to measure left ventricular volume, or liver and kidney volume.

The general method we are using is the reconstruction of an organ from a series of ultrasonic cross-sections taken in an arbitrary fashion. A real-time ultrasonic scanner is coupled to a three-dimensional acoustic position locating system so that the three- dimensional orientation of the scan plane is known at all times. During the patient exam a dedicated microcomputer based data acquisition system is used to record a series of scans over the organ being modelled. The scans are recorded on a video tape recorder before being transferred to a video disk. 3D position information is stored on a floppy disk file. In the proposed system the microprocessor will then be connected to SUMEX where it will become a slave to an AI program running on SUMEX. The SUMEX program will use a model appropriate for the organ which will form the basis of an initial hypothesis about the shape of the organ. This hypothesis will be refined at first by asking the user relevant clinical questions such as (for the fetus) the gestational age, the lie of the fetus in the abdomen and complicating medical factors. This kind of information is the same as that used by the clinician before he even places the scan head on the patient. The model will then be used to request those scans from the video disk which have the best chance of giving useful information. Heuristics based on the protocols used by clinicians during an exam will be incorporated since clinicians tend to collect scans in a manner which gives the most information about the organ. For each requested scan a two-dimensional tolerance region (or plan) derived from the model will be sent to the microcomputer. The requested scan will be retrieved from the video disk, digitized into a frame buffer, and the plan used to direct a border recognition process that will determine the organ outline on the scan. The resulting outline will be sent to SUMEX where it will be used to update the model. The scan requesting process will be continued until it is judged that enough information has been collected. The final model will then be used to determine volume and other quantitative parameters, and will be displayed in three dimensions.

We believe that this hypothesize verify method is similar to that used by clinicians when they perform an ultrasound exam. An initial model, based on clinical evidence and past experience, is present in the clinician's mind even before he begins the exam. During the exam this model is updated by collecting scans in a very specific manner which is known to provide the maximum amount of information. By building an ultrasound imaging system which closely resembles the way a physician thinks we hope to not only

provide a useful diagnostic tool but also to explore very fundamental questions about the way people see.

We are developing this system in phases, starting with an earlier version developed at the University of Washington. During the first phase the previous system was adapted and extended to run in the SUMEX environment. Clinical studies were done to determine its effectiveness in predicting fetal weight. In the second phase computer vision techniques were used to solve some of the problems observed in the clinical trials on the first phase. Further iterations will be tested against clinical data, thus providing valuable feedback for the development process.

B. Medical Relevance and Collaboration

This project is being developed in collaboration with the Ultrasound Division of the Department of Obstetrics at Stanford, of which W.D. McCallum is the director.

Fetal weight is known to be a strong indicator of fetal well-being: small babies generally do more poorly than larger ones. In addition, the rate of growth is an important indicator: fetuses which are "small-for-dates" tend to have higher morbidity and mortality. It is thought that these small-for-dates fetuses may be suffering from placental insufficiency, so that if the diagnosis could be made soon enough early delivery might prevent some of the complications. In addition such growth curves would aid in understanding the normal physiology of the fetus. Several attempts have been made to use ultrasound for predicting fetal weight since ultrasound is painless, noninvasive, and apparently risk-free. These techniques generally use one or two measurements such as abdominal circumference or biparietal diameter in a multiple regression against weight. We recently studied several of these methods and concluded that the most accurate were about +/-200 gms/kg, which is not accurate enough for adequate growth curves (the fetus grows about 200 gms/week). The method we have developed is based on the fact that fetal weight is directly related to volume since the density of fetal tissue is nearly constant. We showed last year that by utilizing three dimensional information more accurate volumes and hence weights can be obtained.

In addition to fetal weight, the first implementation of this system has been evaluated for its ability to determine other organ volumes in vitro. In collaboration with Dr. Richard Popp of the Stanford Division of Cardiology we have evaluated the system on in vitro kidneys and latex molds of the human left ventricle. Left ventricular volumes are routinely obtained by means of cardiac catheterization in order to help characterize left ventricular function. Attempts to determine ventricular volume using one or two dimensional information from ultrasound has not demonstrated the accuracy of angiography. Therefore, three-dimensional information should provide a more accurate means of non-invasively assessing the state of the left ventricle.

C. Highlights of Research Progress

In the last report an initial version of the second phase of program development was described. This version utilizes AI techniques to solve some of the problems encountered with the non-AI system. The prototype system was implemented and tested on two shape classes of balloons (round and long-thin).

For each balloon class a training set of similarly-shaped balloons was used to give the computer knowledge of the given shape. This training set consisted of ultrasonic reconstructions obtained by the previous system. The knowledge was then used to analyze ultrasound data from a similarly-shaped balloon which was not part of the training set. The initial input to the system consisted of the three-dimensional positions

and orientations of a series of ultrasound slices. These slices were previously acquired manually and stored on a video tape recorder. The system was also given the two endpoints of the balloons, which allowed a reference coordinate system to be established. The balloon endpoints interacted with the shape knowledge to define an initial tolerance region, within which the system expected the actual balloon surface to be found. The system's best guess as to the location of the actual balloon surface was the middle of the tolerance region.

Once the initial tolerance region was established an hypothesize-verify paradigm was employed to alternately request a particular ultrasound slice, to provide a tolerance region for an edge detector on that slice, to manually acquire the border of the balloon on that slice, and to update the model by combining the new data with the shape knowledge. This process continued until it was judged that additional slices could contribute no new information.

For an example round balloon (measured volume 267 cc) the initial best guess volume after specifying the endpoints was 242 cc. After one slice best guess volume was 279 cc. After nine slices (out of a possible 30) the system judged that no more slices would be useful: best guess volume was 265 cc. For a different training set of long-thin balloons the final best guess volume for a new reconstruction, after 9 out of a possible 22 slices, was 459 cc, measured volume 461 cc. These results show that learned shape knowledge allowed the system to form a reasonable guess as to the location of the balloon surface even after only two endpoints had been specified.

The major accomplishment this past year was the compilation of the results from this project into the Ph.D. thesis of James Brinkley. In addition the artificial intelligence portion of the system was presented at several meetings, including the student paper competition of the Symposium on Computer Applications in Medicine, where it received the second place award.

Current research is suspended until I find a position following the Ph.D. There is currently some possibility of continuing the research on SUMEX at Stanford.

D. Recent Publications

1. Brinkley, J.F., Muramatsu, S.K., McCallum, W.D. and Popp, R.L.: ***In vitro evaluation of an ultrasonic three-dimensional imaging and volume system.*** Ultrasonic Imaging, 4:126-139, 1982.

2. Brinkley, J.F., McCallum, W.D., Muramatsu, S.K. and Liu, D.Y.: ***Fetal weight estimation from ultrasonic three-dimensional head and trunk reconstructions: Evaluation in vitro.*** Amer. J. Obstet. Gynecol. 144(6):715-721, 1982.

3. Brinkley, J.F., McCallum, W.D., Muramatsu, S.K., and Liu, D.Y.: ***Fetal weight estimation from lengths and volumes found by ultrasonic three-dimensional measurements.*** To be published in *Journal of Ultrasound in Medicine.*

4. Brinkley, J.F.: ***Artificial intelligence and ultrasonic imaging: the use of learned shape knowledge to analyze 3D data.*** Proceedings, 28th Annual Meeting, American Institute of Ultrasound in Medicine, New York, October, 1983.

5. Brinkley, J.F.: ***Learned shape knowledge in ultrasonic three-dimensional organ modelling.*** Second place, student paper competition, Symposium on Computer Applications in Medical Care, Baltimore, October 23-26, 1983.

6. Brinkley, J.F.: *Ultrasonic three-dimensional organ modelling.* Ph.D. Dissertation. Stanford University, to be published as a Stanford Computer Science Technical Report, Spring 1984.

7. Brinkley, J.F.: *Knowledge-driven ultrasonic three-dimensional organ modelling.* Submitted to *IEEE Trans. Pattern Analysis and Machine Intelligence.*

E. Funding Support

"Ultrasonic Three-dimensional Organ Modelling", individual postdoctoral fellowship. Fellow: James F. Brinkley Sponsor: W.D. McCallum Funding Agency: National Institute of General Medical Sciences Number: 1 F32 GM08092 Total term and direct cost: 7/1/81-6/30/84 (3 years) $55,452 (stipend) Current funding from this fellowship: 7/1/83-6/30/84 (1 year) $19,716

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Collaborations

We are collaborating more with medical people than anyone else. The project is located in the Obstetrics Department at Stanford where W.D. McCallum manages the ultrasound patients. We have also been collaborating with Dr. Richard Popp in the Division of Cardiology at Stanford.

B. Sharing and Interactions with SUMEX projects

Mostly personal contacts with the Heuristic Programming Project and Medical Information Science Program at Stanford. The message facilities of SUMEX have been especially useful for maintaining these contacts. Since the first phase of the project is now essentially complete we have been interacting more with other SUMEX projects in order to develop the AI ideas.

C. Critique of Resource Management

In general SUMEX has been a very usable system, and the staff has been very helpful.

III. RESEARCH PLANS

A. Project Goals and Plans

The major conclusion from the research leading to the Ph.D. is that the current hardware we use for three-dimensional location is not accurate enough to permit further work on organ modelling. For this reason I have proposed several alternative methods of utilizing 3D medical image data, including 3D CT, NMR or ultrasound. All these modalities produce 3D arrays of data which would be much easier to use than arbitrary slices.

Given this type of data, fairly straightforward extensions of the model representation developed for balloons could be used for the heart or kidney. The basic idea would be to have the human operator indicate three organ landmarks within the 3D data, then let the computer utilize learned shape knowledge to selectively "biopsy" portions of the 3D data in order to define the actual organ instance. Since the data would be available as a 3D array, the edge detection process could take place along a one-

dimensional tolerance region rather than on a two-dimensional slice. Since all forms of medical images are becoming available as 3D arrays this seems like a better approach than the selection of individual slices.

Depending on the interest of engineers in providing 3D data much of the AI modelling could still be done on SUMEX. Many of the AI techniques could also be developed for 2D images for knowledge-driven border detection.

B. Justification and requirements for continued SUMEX use

The goals of this project seem to be compatible with the general goals of SUMEX, i.e., to develop the uses of artificial intelligence in medicine. The problem of three-dimensional modelling is a very general one which is probably at the heart of our ability to see. By developing a medical imaging system that models the way clinicians approach a patient we should not only develop a useful clinical tool but also explore some very fundamental problems in AI.

The availability of a large well supported facility like SUMEX has been and will continue to be very valuable as we develop and test further implementations of the system. Our current share of the SUMEX resources is adequate.

C. Needs and plans for other computing resources beyond SUMEX-AIM

Judging from our present experience it appears that SUMEX could not handle the amount of data required for image processing on digitized ultrasound scans. This is one of the main reasons we are proposing a distributed system in which SUMEX only directs a smaller machine to do the actual number crunching. It is also one of the reasons we are postponing direct digitization until later. As microprocessors become more powerful they will be capable of acting as slaves to an intelligent SUMEX program. The AI program will direct the image processing functions of the micro so that the data is processed in an intelligent way, but SUMEX will only see the results of that processing, not the actual data. We will thus need to keep track of developments in microcomputers so that we can develop this kind of distributed system.

An additional problem is the small address space of the 2060. Attempts will be made to optimize the code, but this could become a major problem in the future. A better solution might be an image processing workstation with a large address space.

D. Recommendations

Since we are planning to develop a distributed system we would hope to see these kind of systems being developed by the SUMEX resource. Projects that would be of direct interest are networks (such as ETHERNET), personal computer stations, graphics displays, etc.

II.A.4. Pilot AIM Projects

Following is a description of the informal pilot project currently using the AIM portion of the SUMEX-AIM resource, pending funding, full review, and authorization.

In addition to the progress report presented here, an abstract is submitted on a separate Scientific Subproject Form.

II.A.4.1. PATHFINDER Project

PATHFINDER Project

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City of Hope National Medical Center
Duarte, California

Lawrence M. Fagan, M.D., Ph.D.
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Stanford University

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

Our project addresses difficulties in the diagnosis of lymph node pathology. Five studies from cooperative oncology groups have documented that, while experts show good agreement with one another, the diagnosis made by practicing pathologists may have to be changed by expert hematopathologists in as many as 50% of the cases. Precise diagnoses are crucial for the determination of optimal treatment. To make the knowledge and diagnostic reasoning capabilities of experts available to the practicing pathologist, we have developed a pilot computer-based diagnostic program called PATHFINDER. The project is a collaborative effort of the City of Hope National Medical Center and the Stanford University Medical Computer Science Group. A pilot version of the program provides diagnostic advice on 45 common benign and malignant diseases of the lymph node based on 77 histologic features. Our research plans are to develop a full-scale version of the computer program by substantially increasing the quantity and quality of knowledge and to develop techniques for knowledge representation and manipulation appropriate to this application area. The design of the program has been strongly influenced by the INTERNIST/CADUCEUS program developed on the SUMEX resource.

A group of expert pathologists from several sites in the U.S., have agreed to help build the knowledge base for the PATHFINDER program. Each will independently provide the entire knowledge in incremental stages after agreement has been obtained on the design aspects. We estimate that the final version of the program will include about 80 diseases and 175 features.

B. Medical Relevance and Collaboration

One of the most difficult areas in surgical pathology is the microscopic interpretation of lymph node biopsies. Most pathologists have difficulty in accurately classifying lymphomas. Several cooperative oncology group studies have documented that while experts show good agreement with one another, the diagnosis rendered by a "local" pathologist may have to be changed by expert lymph node pathologists (expert hematopathologists) in as many as 50% of the cases.

The National Cancer Institute recognized this problem in 1968 and created the Lymphoma Task Force which is now identified as the Repository Center and the Pathology Panel for Lymphoma Clinical Studies. The main function of this expert panel

of pathologists is to confirm the diagnosis of the "local" pathologists and to ensure that the pathologic diagnosis is made uniform from one center to another so that the comparative results of clinical therapeutic trials on lymphoma patients are valid. An expert panel approach is only a partial answer to this problem. The panel is useful in only a small percentage (3%) of cases; the Pathology Panel annually reviews only 1,000 cases whereas more than 30,000 new cases of lymphomas are reported each year. A Panel approach to diagnosis is not practical and lymph node pathology cannot be routinely practiced in this manner.

We believe that practicing pathologists do not see enough case material to maintain a high-level of diagnostic accuracy. The disparity between the experience of expert hematopathology teams and those in community hospitals is striking. An experienced hematopathology team may review thousands of cases per year. In contrast, in a community hospital, an average of only 10 new cases of malignant lymphomas are diagnosed each year. Even in a university hospital, only approximately 100 new patients are diagnosed every year.

Because of the limited numbers of cases seen, pathologists may not be conversant with the differential diagnoses consistent with each of the histologic features of the lymph node; they may lack familiarity with the complete spectrum of the histologic findings associated with a wide range of diseases. In addition, pathologists may be unable to fully comprehend the conflicting concepts and terminology of the different classifications of non-Hodgkin's lymphomas, and may not be cognizant of the significance of the immunologic, cell kinetic, cytogenetic, and immunogenetic data associated with each of the subtypes of the non-Hodgkin's lymphomas.

In order to promote the accuracy of the knowledge base development we will have participants for multiple institutions collaborating on the project. Dr. Nathwani will be joined by experts from Stanford (Dr. Dorfman), St. Jude's Children's Research Center -- Memphis (Dr. Berard) and City of Hope (Dr. Burke).

C. Highlights of Research Progress

C.1 Accomplishments This Past Year

Since the project's inception in November, 1983, we have constructed several versions of PATHFINDER. The first several versions of the program were ***rule-based*** systems like MYCIN and ONCOCIN which were developed earlier in the Stanford group. We soon discovered, however, that the large number of overlapping features in diseases of the lymph node would make a rule-based system cumbersome to implement. We next considered the construction of a ***hybrid system***, consisting of a rule-based algorithm that would pass control to an INTERNIST-like scoring algorithm if it could not confirm the existence of classical sets of features. We finally decided that a modified form of the INTERNIST program would be most appropriate. The current version of PATHFINDER is written in the computer language Maclisp and runs on the SUMEX DEC-20.

C.1 The PATHFINDER knowledge base

The basic building block of the PATHFINDER knowledge base is the disease profile or ***frame***. The disease frame consists of ***features*** useful for diagnosis of lymph node diseases. Currently these features include histopathologic findings seen in both low- and high-power magnifications. Each feature is associated with a list of exhaustive and mutually exclusive ***values***. For example, the feature ***pseudofollicularity*** can take on any one of the values ***absent***, ***slight***, ***moderate***, or ***prominent***. These lists of values give the program access to ***severity*** information. In addition, these lists eliminate obvious

interdependencies among the values for a given feature. For example, if pseudofollicularity is ***moderate***, it cannot also be ***absent***.

Evoking strengths and frequencies are associated with each feature-value pair in a disease profile. We are experimenting with different scales for scoring each feature-value pair, and several methods for combining the scores to form a differential diagnosis. A disease-independent import is also assigned to each feature-value but only a two-valued scale is used. This is because, in PATHFINDER, imports are only used to make boolean or yes/no decisions (see below). In addition to import, PATHFINDER utilizes the concept of ***classic*** features for a disease -- within each disease frame, the pathologist marks those feature-value pairs which are considered to be part of the classic pattern of the disease.

The PATHFINDER knowledge base contains information about obvious association between features. This information is of the form: "Don't ask about feature x unless feature y has certain values." For example, it wouldn't make sense to ask about the degree or range of follicularity if there are no follicles in the tissue section. The feature links also serve to identify interdependencies among features. Feature interdependence is a problem because it can lead to inaccuracies in scoring hypotheses.

The prototype knowledge base was constructed by Dr. Nathwani. During the beginning part of 1984, we organized two meetings of the entire team of experts to define the selection of diseases to be included in the system, and the choice of features to be used in the scoring process. After the features are defined (with text, diagrams, and/or slides) we will proceed with the scoring process.

D. Publications Since January 1983

No publications directly related to PATHFINDER. See publications under ONCOCIN for a selection of recent papers by the computer science collaborators.

E. Funding Support

Research Grant submitted to National Institutes of Health, March, 1984.

Grant Title:"Computer-aided Diagnosis of Malignant Lymph Node Diseases"
Principal Investigator: Bharat Nathwani

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations and Program Dissemination via SUMEX

Because our team of experts are in different parts of the country and the computer scientists are not located at the City of Hope, we envision a tremendous use of SUMEX for communication, demonstration of programs, and remote modification of the knowledge base. The proposal mentioned above was developed using the communication facilities of SUMEX.

B. Sharing and Interaction with Other SUMEX-AIM Projects

Our project depends heavily on the techniques developed by the INTERNIST/CADUCEUS project. Although we have not as yet had direct contacts with the group since the start of the PATHFINDER project, we have been able to utilize information and experience with the INTERNIST program gathered over the years through the AIM conferences and on-line interaction. We expect to re-establish these

contacts in the near future. Our experience with the extensive development of the pathology knowledge base utilizing multiple experts should provide for intense and helpful discussions between our two projects.

C. Critique of Resource Management

The SUMEX resource has provided an excellent basis for the development of a pilot project. The availability of a pre-existing facility with appropriate computer languages, communication facilities (especially the TYMNET network), and document preparation facilities allowed us to make good progress in a short period of time. The management has been very useful in assisting with our needs during the start of this project.

III. RESEARCH PLANS

A. Project Goals and Plans

Collection and refinement of knowledge about lymph node pathology

The pilot computer program suggests diagnosis on 45 common diseases of the lymph node (18 benign, 26 primary malignant, and 1 metastatic) based on 77 histologic features. We plan to dramatically increase quantitatively and qualitatively the knowledge base of the system. We will explore the problems of combining knowledge bases created by multiple experts, but based on a common framework.

We also plan to develop techniques for simplifying the acquisition and verification of knowledge from experts, create mapping schemes that will facilitate the understanding of the many classifications of non-Hodgkin's lymphomas. We will also attempt to represent knowledge about special diagnostic entities, such as multiple discordant histologies and atypical proliferations, which do not fit into the classification methods we have utilized.

Representation Research

We hope to enhance the INTERNIST-1 model by structuring features into a useful hierarchy, implementing new methods for scoring hypotheses, creating appropriate explanation capabilities, and formulating and applying high-level heuristics to guide the program.

B. Requirements for Continued SUMEX Use

We are currently dependent on the SUMEX computer for the development of the program. We are in the process of transferring the program over to Portable Standard Lisp, which can then be transferred to the HP9836 workstations available in the Medical Computer Science Group at Stanford. While the switch to workstations will lessen our requirements for computer time for the development of the algorithms, we will continue to need the SUMEX facility for the interaction with each of the research locations specified in our NIH proposal. The HP equipment is currently unable to allow remote access, and thus the program will have to be maintained on the 2060 for use by all non-Stanford users.

C. Requirements for Additional Computing Resources

Most of our computing resources will be met by the 2060 plus the use of the HP9836 workstation. We will need additional file space on the 2060 as we quadruple the size of our knowledge base. We will continue to require access to the 2060 for communication purposes, access to other programs, and for file storage and archiving.

D. Recommendations for Future Community and Resource Development

We encourage the continued exploration by SUMEX of the interconnection of workstations within the mainframe computer setting. We will need to be able to quickly move a program from workstation to workstation, or from workstation back and forth to the mainframe. Software tools that would help the transfer of programs from one type of workstation to another would also be quite useful.

National AIM Project: Computer-Aided Diagnosis of Malignant Lymph Node Diseases

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We are building a computer program, called PATHFINDER, to assist in the diagnosis of lymph node pathology. The project is based at the City of Hope National medical center in collaboration with the Stanford University Medical Computer Science Group. A pilot version of the program provides diagnostic advice on 45 common benign and malignant diseases of the lymph node based on 77 histologic features. Our research plans are to develop a full-scale version of the computer program by substantially increasing the quantity and quality of knowledge and to develop techniques for knowledge representation and manipulation appropriate to this application area. The design of the program has been strongly influenced by the INTERNIST/CADUCEUS program developed on the SUMEX resource.

SOFTWARE AVAILABLE ON SUMEX

PATHFINDER-- A version of the PATHFINDER program is available for experimentation on the DEC 2060 computer. This version is a pilot version of the program, and therefore has not been completely tested.

II.A.4.2. RXDX Project

RXDX Project

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I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

We are developing a prototype expert system that could act as a consultant in the diagnosis and management of depression. Health professionals would interact with the program as they might with a human consultant, describing the patient, receiving advice, and asking the consultant about the rationale for each recommendation. The program will use a knowledge base constructed by encoding the clinical expertise of a skilled psychiatrist in a set of rules. It will use this knowledge base to decide on the most likely diagnosis (endogenous or nonendogenous depression), assess the need for hospitalization, and recommend specific somatic treatments when this is indicated (e.g., tricyclic antidepressants). The treatment recommendation will take into account the patient's diagnosis, age, concurrent illnesses, and concurrent treatments (drug interactions).

B. Medical Relevance and Collaboration

There has been a growing emphasis in American psychiatry on careful diagnosis using clearly defined clinical criteria (Feighner, et al., 1972; Spitzer, et al., 1975, 1980; Feinberg and Carroll, 1982, 1983). These efforts have led to several sets of criteria for the diagnosis of psychiatric disorders. The "St. Louis" criteria (Feighner, et al., 1972) were succeeded by the Research Diagnostic Criteria (RDC), formulated by researchers from St. Louis and New York (Spitzer, et al., 1975). The RDC led directly to the criteria that are now quasi-official in American psychiatry, DSM-III (Spitzer, et al., 1980). All of these criteria lists were based on a combination of clinical opinion and literature review, and use a decision-tree approach to making a diagnosis. These diagnostic systems have been shown to be acceptably reliable, but their validity remains untested. Other groups have used a multivariate statistical approach to diagnosis. Roth and his colleagues (Carney, et al., 1965) published a discriminant index for distinguishing "endogenous" from "neurotic" depressed patients. This work was repeated by Kiloh, et al. (1972) with much the same results, confirming the findings of Carney, et al. (1965).

We have done similar work, deriving two discriminant indices for separating endogenous depressed patients (unipolar or bipolar) from nonendogenous (neurotic) patients. We cross-validated these indices in separate groups of patients, and also validated them against an external standard, the dexamethasone suppression test (Feinberg and Carroll, 1982, 1983). At the same time, we and others have been further

developing this and other biological measures that may differentiate between patients with endogenous and nonendogenous depression. These include neuroendocrine tests such as the dexamethasone suppression test (DST) and quantitative studies of sleep using EEG. Carroll, et al. (1981) have shown that the DST is abnormal in about 67% of patients with endogenous depression (melancholia) and only 5-10% with nonendogenous (neurotic) depression. Kupfer, et al. (1978) and Feinberg, et al. (1982) have similar results with EEG studies of sleep. These biological markers may be useful for routine clinical use, and can certainly be used as external validating criteria to test the performance of different clinical diagnostic methods, including those mentioned above. Furthermore, we have developed biological criteria for "definitely endogenous" depression and "definitely nonendogenous" depression based on DST and sleep EEG. (Carroll, et al., 1980). Our goal is to use these criteria as an external validating criterion for assessing the performance of various new or different diagnostic schemes, in particular an expert system of the sort we are developing.

C. Highlights of Research Progress

This project began in November 1983. We have been examining two other SUMEX-based psychiatry projects, the BLUEBOX project of Mulsant and Servan-Schreiber (1984), and the HEADMED project of Heiser and Brooks (1978, 1980). Mulsant and Servan-Schreiber visited us at Michigan and discussed the rationale and progress of their project. Heiser also visited with us and has agreed to collaborate with our project as a consultant. He is working on psychopharmacology and is attempting to develop and integrate an appropriate knowledge base for our system.

At Michigan, we have encoded most of the Hamilton Rating Scale (Hamilton, 1967) into EMYCIN rules. This is the standard scale (in English) for rating the severity of depression, and many of the items in it will be relevant to our consultant program. We expect to finish this subproject within the next few weeks.

We have begun to collect video recordings of patient interviews. We select patients recently admitted to the University of Michigan Clinical Studies Unit. They are interviewed by Feinberg and the interviews are observed by Lindsay plus a group of psychiatric residents, psychiatrists and psychologists. After the interview, Feinberg is debriefed by Lindsay, and then the others discuss the case. These data will be the initial source of the expert knowledge base for our consultant.

D. List of Relevant Publications

This project has not yet produced any publications. The following list contains the references cited above, including our previous publications relevant to the RxDx project.

1. Carney, M. W. P., Roth, M. and Garside, R. F.:*The diagnosis of depressive syndromes and the prediction of ECT response*, Brit. J. Psychiatry, 111, 659-674, 1965.

2. Carroll, B. J., Feinberg, M., Greden, J. F., Haskett, R. F., James, N. McI., Steiner, M., and Tarika, J. *Diagnosis of endogenous depression: Comparison of clinical, research, and neuroendocrine criteria*, J. Affect Dis., 2, 177-194, 1980.

3. Carroll, B. J., Feinberg, M., Greden, J. F., Tarika, J., Albala, A. A., Haskett, R. F., James, N. McI., Kronfol, Z., Lohr, N., Steiner, M., de Vigne, J-P, and Young, E.:*A specific laboratory test for the diagnosis of melancholia*, Standardization, validation, and clinical utility. Arch. Gen. Psychiatry, 38, 15-22, 1981.

4. Feighner, J. P., Robins, E., Guze, S. B., Woodruff, R. A., Winokur, G., and Munoz, R.: *Diagnostic criteria for use in psychiatric research*, Arch. Gen. Psychiatry, 26, 57-63, 1972.

5. Feinberg, M. and Carroll, B. J.: *Separation of subtypes of depression using discriminant analysis: I. Separation of unipolar endogenous depression from non-endogenous depression*, Brit. J. Psychiatry, 140, 384-391, 1982.

6. Feinberg, M. and Carroll, B. J.:*Separation of subtypes of depression using discriminant analysis. II. Separation of bipolar endogenous depression from nonendogenous ("neurotic") depression*, J. Affective Disorders, 5, 129-139, 1983.

7. Feinberg, M. and Carroll, B.J.: *Biological markers for endogenous depression in series and parallel*, Biological Psychiatry 19:3-11, 1984.

8. Feinberg, M. and Carroll, B.J.: *Biological and nonbiological depression*, Presented at Annual Meeting of the Society of Biological Psychiatry, Los Angeles, May, 1984, Abstract #81.

9. Feinberg, M., Gillin, J. C., Carroll, B. J., Greden, J. F., and Zis, A. P.:*EEG studies of sleep in the diagnosis of depression* Biological Psychiatry, 17, 305-316, 1982.

10. Heiser, J. F. and Brooks, R. E.:*Design considerations for a clinical psychopharmacology advisor*, Proc. Second Annual Symp. on Computer Applications in Medical Care. New York: IEEE, 1978, 278-285.

11. Heiser, J. F. and Brooks, R. E.:*Some experience with transferring the MYCIN system to a new domain*, IEEE Trans. on Pattern Analysis and Machine Intelligence, PAMI-2, No. 5, 477-478, 1980.

12. Kiloh, L. G., Andrews, G., and Neilson, M.:*The relationship of the syndromes called endogenous and neurotic depression*, Brit. J. Psychiatry, 121, 183-196, 1972.

13. Kupfer, D. J., Foster, F. G., Coble, P., McPartland, R. J., and Ulrich, R. F.:*The application of EEG sleep for the differential diagnosis of affective disorders*, Am. J. Psychiatry, 135, 69-74, 1978.

14. Mulsant, B. and Servan-Schreiber, D.:*Knowledge engineering: A daily activity on a hospital ward*, Computers in Biomedical Research, 1984.

15. Spitzer, R. L., Endicott, J. and Robins, E.: *Research diagnostic criteria*, (2d ed.) New York State Department of Mental Hygiene, New York Psychiatric Institute, Biometrics Research Division, 1975.

16. Spitzer, R. L.: (Ed.).*Diagnostic and statistical manual of mental disorders*, (3d ed.). Washington, D. C.: American Psychiatric Association, 1980.

17. Van Melle, W.:*The EMYCIN Manual*, Computer Science Department, Stanford University, Report HPP-81-16, 1981.

E. Funding Support

We have submitted an application for support to the Vice-President for Research at the Univ of Michigan, who has funds for "seed money" for faculty research (Total

Direct Costs = $3215). We have prepared a grant application, to be sent to the NIH "Small Grants" Program for the May 1, 1984 deadline (Total Direct Costs = $13,850). These funds should enable us to gather the pilot data we will need as part of a major grant application.

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaboration and Program Dissemination via SUMEX

We are collaborating via SUMEX with Dr. Jon Heiser, who worked with Ruven Brooks on HEADMED in the late 1970's. We are sharing a common SUMEX account, and communicating using computer mail. Dr. Heiser will write the section of the expert system dealing with the treatment of depression (and eventually of other psychiatric disorders) while Drs. Feinberg and Lindsay work on the diagnostic parts of the system.

B. Sharing and Collaboration with other SUMEX-AIM Projects

We are also collaborating, although more loosely, with Messrs. Benoit Mulsant and David Servan-Schreiber. They wrote an expert system (BLUEBOX) for the diagnosis and treatment of depression which was a first step in the direction we are going. We have access to BLUEBOX through SUMEX, and have been able to learn from its successes and failures. Ben and David will, we expect, be able to offer us many helpful suggestions on our expert system (RXDX) as they pursue their training in Psychiatry and continue their work in AI in medicine.

C. Critique of Resource Management

We have been using EMYCIN to set up our knowledge base, and have found this program invaluable, since it has saved us many hours of programming in LISP. There are some problems with EMYCIN, many of which center around discrepancies between the the version of EMYCIN described in the manual and the version actually running on SUMEX. We would suggest that EMYCIN be more strongly supported than is now the case, if it and SUMEX are to be even more useful to beginners in AI in Medicine. This may involve added expense, such as would be involved in the purchase of an updated version of EMYCIN, but we would certainly be able to make use of the updated version.

SUMEX itself has been invaluable. We don't have easy access to any other machine of equal computing power which also has a strongly supported LISP available. Specifically, the Dandelion LISP machine at Michigan is not easily accessible, while the LISP compiler available on the Amdahl 5860 here differs from those used at major AI centers such as Stanford and MIT. We have also made good use of the ARPANET connections that SUMEX offers. Feinberg will spend a month of his sabbatical working with Prof. Peter Szolovits at MIT, learning about AI in Medicine. (This is an obvious and necessary step for any physician wanting to begin work in the field.) This visit was arranged using computer mail through SUMEX. Lindsay and Feinberg will be able to continue their collaborative work while the latter is in Cambridge, using the same medium. The alternative would be days lost in the mails and many dollars spent on phone calls. We have also been able to get rapid help with problems that arise with EMYCIN using computer mail, saving days and/or dollars.

III. RESEARCH PLAN

A. Project Goals and Plans

Our immediate objective is to develop an expert system which can differentiate patients with the various subtypes of depressive disorder, and prescribe appropriate